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Atrial natriuretic factor

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

1994

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Janssen, W. M. T. (1994). *Atrial natriuretic factor: integrated effects on blood pressure, natriuresis, and renal medullary blood flow in man*. s.n.

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CHAPTER 1

INTRODUCTION

Chapter 1

History probably will never reveal why it lasted till 1981 before de Bold et al [1] described the existence of a 28-amino acid protein of cardiac origin with antihypertensive and natriuretic properties, which accordingly was named the atrial natriuretic factor (ANF) [2]. Indeed, the presence of granules in cardiac myocytes as well as the depletion of these granules after extracellular volume expansion were already observed in 1956 [3,4]. Moreover, an important relationship between changes in extracellular volume and urinary sodium excretion was already noted in the fifties [5,6]. In the sixties, many studies were performed to elucidate the mechanism of this relationship. Several mechanisms were proposed such as dilutional effects, changes in renal medullary blood flow or the existence of a "third factor", or "natriuretic hormone" that would mediate extracellular volume-induced natriuresis apart from glomerular filtration rate and aldosterone [7-8]. However, most of these hypotheses could not be tested directly, until the discovery of ANF by de Bold et al offered a clue to the long searched solution of the puzzle of the relation between extracellular volume and urinary sodium excretion. Thereafter, the scientific and pharmaceutical communities threw themselves into the elucidation of the (physiological) significance of ANF as if to make up for lost time.

In animal studies ANF was shown to decrease blood pressure, to increase urinary sodium excretion and glomerular filtration rate, to increase or decrease renal blood flow, and to suppress several elements of the renin-angiotensin-aldosterone axis [1,9-10]. The mechanism of the ANF-induced natriuresis remained debated. Some investigators forwarded the rise in glomerular filtration rate to be the main cause of natriuresis [11]. Others focused on a direct tubular action of ANF. Numerous in vitro and in vivo animal studies implied or denied the main site to be the proximal tubule, Henle's loop or the inner medullary collecting duct [12-15]. Moreover, an increase in renal medullary blood flow was shown to be a possible important mechanism of the natriuretic action of ANF [10]. An ANF-induced increase in renal medullary blood flow was suggested by studies directly measuring the effects of ANF on medullary blood flow using diverse techniques [10,16]. ANF was suggested to cause a washout of the medullary interstitium, and to increase renal interstitial pressure, which both are recognized to be related to increases in renal medullary blood flow [9,17-19]. At this point in time, we and others started to study the systemic and renal effects of ANF in man. Effects of ANF on blood pressure, urinary sodium excretion, glomerular filtration rate, effective renal plasma flow and the renin-angiotensin-aldosterone system (RAAS) could be measured directly. The possible effects of ANF in man on proximal and/or distal tubular segments and on medullary blood flow however, had to be estimated indirectly from free water and lithium clearance techniques and from changes in urinary osmolality. Direct measurements of changes in medullary blood flow, which might be an important mechanism to influence urinary excretion of sodium for other hormones than ANF as well, were at that time impossible to perform in man.

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In Groningen, Navis, and before her Hoorntje and Prins had worked on the renin-angiotensin-aldosterone system, studying in particular the natriuretic and systemic hemodynamic effects of angiotensin-converting-enzyme-inhibitors (ACEi) [20-22]. In this respect studies with ANF, known to counteract the RAAS [9], seemed logical. In the studies with ACEi special attention was given to the chronic effects of ACEi. Therefore, and because ANF seemed to be a continuously circulating hormone [23], we designed our studies to investigate the effects of long-term continuously infused ANF. At the time when we started working with ANF in Groningen in 1986 only a few studies were available on the effects of ANF in humans. Weidmann et al had described the results of short-term infusions of ANF in normal volunteers. Blood pressure fell, whereas sodium excretion increased. They further observed a rise in glomerular filtration rate with a concomitant slight decrease in effective renal plasma flow [24]. Richards et al observed similar effects with bolus injections of ANF [25]. Our first studies (Section I, chapters 3-5) therefore were addressed to evaluate the effects of different (long-term) infusion durations and (low) doses of ANF on systemic blood pressure and natriuresis.

The studies in Section II were focussed on the natriuretic mechanism of ANF in man. The first 2 studies in this Section (chapters 6 and 7) were addressed to the tubular versus hemodynamic effects of ANF, and to the importance of blood pressure for ANF-induced natriuresis in particular. The tubular site(s) of action of ANF were evaluated with the use of free water clearance techniques (chapter 6). In particular, the study was designed to assess a possible (medullary) tubular site of action of ANF, since pressure related natriuretic effects are thought to affect sodium transport in the proximal tubule and/or loop of Henle [26,27]. To elaborate the importance of blood pressure for ANF-induced sodium excretion further, the relation between the diurnal rhythms of blood pressure and urinary sodium excretion as well as the effect of ANF on this relationship were evaluated in patients with essential hypertension (chapter 7). Since the mechanism of the ANF-induced natriuresis had also been associated with (intra)renal hemodynamic changes we designed the last studies of this thesis (chapters 8-10) to offer more insight in the effects of ANF on total renal blood flow and intrarenal blood flow distribution in man. Whereas in general in many animal studies ANF was shown to increase renal blood flow, in man ANF caused effective renal plasma flow to decrease. Since measurements of effective renal plasma flow do not account for possible changes in hematocrit and the renal extraction of hippuran, we measured the effects of ANF on these parameters, thus being able to calculate ANF-induced changes in total renal blood flow (chapter 8). In a further study the effects of ANF on intrarenal hemodynamic function was explored. To be able to measure non-invasively and directly (changes in) renal medullary blood flow in man a new method was developed based on the kinetic modeling of ¹²³I-hippuran renography. This method was evaluated in dogs (chapter 9), and was finally applied to human renography data to test the hypothesis that ANF predominantly decreases cortical blood flow and might increase renal medullary blood flow (chapter 10).

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Chapter 2 gives a general overview over studies in literature dealing with the (patho)physiological significance of ANF. The thesis ends with a summary and look to the future (chapter 11).

In summary, in this thesis the following questions will be addressed:

1. what are the effects of different long-term infusion durations of low doses ANF on blood pressure and urinary sodium excretion ?
2. what is the mechanism of the ANF-induced natriuresis in man:
 - does ANF induce an increase in GFR ?
 - does ANF inhibit (proximal and/or distal) tubular sodium reabsorption ?
 - are there indications for a blood pressure dependent mechanism of ANF-induced natriuresis ?
 - does ANF interfere with the RAAS ?
 - does ANF induce an increase in renal medullary blood flow ?

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